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Partial cross-enhancement in models for dengue epidemiology

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HIGHLIGHTS

- Cross-enhancement between serotypes a key factor in dengue epidemiology.
- Reappraisal of data suggests cross-enhancement only affects small number of cases.
- Conventional model framework for cross-enhancement revised.
- If enhancement rare, high intensity required to generate multi-annual oscillations.
- Oscillations generated by other drivers modified by enhancement even if rare.

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ABSTRACT

Four distinct serotypes of dengue virus co-circulate in many parts of the world. Antibodies to one serotype prevent infection with the homologous serotype, but may enhance infections with heterologous serotypes. Enhanced secondary infections have been implicated in the majority of severe cases, termed dengue hemorrhagic fever. Conventionally, mathematical models assume that all heterologous secondary infections are subject to enhanced susceptibility or transmissibility. However, empirical data show that only a minority of secondary infections lead to severe disease, which suggests that only a minority of secondary infections are subject to enhancement. We present a new modelling framework in which the population susceptible to secondary infection is split into a group prone to enhanced infection and a group with some degree of cross-protection. We use this framework to re-evaluate the role of enhanced infections in several well known dengue models that exhibit multi-annual epidemiological oscillations. We show that enhancement is unlikely to be driving such oscillations but may be modifying the effects of other drivers.

1. Introduction

Dengue is a mosquito-borne virus that infects people throughout tropical and subtropical regions. It causes dengue fever and a more severe form, dengue hemorrhagic fever (DHF). It is estimated that over 2.5 billion people are at risk (World Health Organization, 2012) and that there are 390 million dengue infections per year (Bhatt et al., 2013). There are four distinct serotypes of dengue, DENV-1, 2, 3, 4. In hyper-endemic regions the prevalence of each serotype is oscillatory with an 8–10 year cycle (Nisalak et al., 2003; Recker et al., 2009). The epidemiological dynamics of the four serotypes are interwoven by immune cross-reaction. Infection with any serotype results in long-term homologous immunity and probably a short period of heterologous immunity (Sabin, 1952; Reich et al., 2013). As this heterologous immunity wanes, antibody-dependent enhancement (ADE) may occur when non-neutralising antibodies bind to infecting viruses and facilitate cell entry. The intracellular antiviral response may also be compromised. Consequently ADE accelerates viral production, potentially leading to higher viremia and more severe disease. See Guzman and Vazquez (2010) for a review of the ADE mechanism in dengue. Heterologous secondary infections are implicated in the majority of dengue hemorrhagic fever (DHF) cases (Gubler and Kuno, 2004).

The standard framework for incorporating ADE into epidemiological models assumes that all individuals that experience a primary infection then become prone to an enhanced secondary infection. This enhancement may act by increasing susceptibility to infection (due to the facilitation of viral entry) and/or increasing transmission once infection has occurred and/or increasing the mortality associated with infection (both due to higher viremia). In the standard modelling framework, enhanced secondary infections can drive compelling epidemiological dynamics. The impact

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is similar whether enhancement acts through susceptibility or transmission (Ferguson and Andreasen, 2002; Adams and Boots, 2006). Pioneering mathematical modelling studies showed that in an unforced two serotype system a relatively small degree of transmissibility enhancement in secondary infections can result in periodic or chaotic dynamics with recurrent epidemics each spanning several years (Ferguson et al., 1999a). It was consequently suggested that ADE may be driving similar underlying multi-annual epidemiological oscillations observed in dengue prevalence data. Many studies have explored the phenomenon of these 'enhancement-induced' oscillations (Aguiar et al., 2011), documenting fascinating dynamics for a range of epidemiological conditions (Ferguson and Andreasen, 2002; Schwartz et al., 2005; Adams and Boots, 2006; Billings et al., 2007; Bianco et al., 2009; Recker et al., 2009; Wikramaratna et al., 2010). Other research has used similar frameworks to model enhancement but investigated alternatives to ADE that may be driving epidemiological oscillations. Stochastic seasonal variation in transmission can sustain long period oscillations in prevalence, with immune cross-reaction between serotypes determining the phase relationship between the time series of their prevalences (Adams et al., 2006). Complete but temporary heterologous cross-protection can lead to 'immunity-induced' oscillatory dynamics in systems where secondary infections are enhanced or neutral (Wearing and Rohani, 2006), or even have reduced transmissibility if severe disease associated with enhanced infection results in rapid hospitalisation (Aguiar et al., 2008, 2011).

These conventional frameworks assume that all secondary infections are enhanced. However, in an outbreak of DENV-2 in Cuba in 1997 only 2–4% of individuals with a secondary infection had DHF. Genetic predisposition was implicated as a risk factor (Guzmán et al., 2002; Guzmán and Kouri, 2002). A cohort study of children in Thailand from 2006 to 2009 found that 96% of DHF cases had secondary infections, but only 13% of secondary infections were DHF cases (Sabchareon et al., 2012). A sample of 1009 children in Thailand in 1980 found multitypic seroconversion in 80% of 10–11 year olds (Sangkawibha et al., 1984; Ferguson et al., 1999b); it is unlikely that such a large proportion also experienced DHF. Antibody dependent enhancement may occur without leading to DHF. However, given that accelerated viral replication underlies the enhancement of susceptibility, transmission and disease severity, the prevalence of DHF is likely to be a reasonable estimate for the prevalence of ADE.

These empirical observations lead us to propose a new framework for modelling antibody-dependent enhancement of dengue. In this framework, the population susceptible to secondary infections is split into a group prone to enhancement, and a group that is not prone to enhancement and may have some degree of protection with respect to secondary infection. We introduce this framework as a generalisation of the conventional two serotype model (Ferguson et al., 1999a). With reference to the conventional model we explore how ADE prevalence and ADE intensity combine to determine the absence or occurrence of oscillatory dynamics. We then investigate how the new framework for ADE affects the behaviour of long period oscillations in a model with stochastic seasonality (Adams et al., 2006) and a model with temporary heterologous cross-immunity (Wearing and Rohani, 2006; Aguiar et al., 2011). It is not our purpose to compare these models with one another in terms of their capacity to replicate the epidemiological dynamics of dengue. Rather, we have chosen these models as representative examples of the main approaches to modelling epidemiological oscillations induced by immune cross-reaction, and our purpose is to assess the impact of refining the model framework for cross-enhancement in each of these contexts.

Mathematical modelling is a key part of modern epidemic control analysis. The core of any dengue model is likely to be similar to one of the frameworks we consider here. These models may be used to assess how key properties of the epidemiological dynamics, for instance prevalence or periodicity, are affected by intervention or contextual modification, for instance vaccines, vaccine administration programmes, climate changes or the emergence of new serotypes. Enhanced infections are a key component of dengue epidemiology and so need to be modelled correctly. Here we argue that this may require some modification of the conventional framework for modelling enhancement. We focus on the role of enhancement in long period epidemic cycles. We show that models with the same 'average' cross-reaction in the population behave similarly. But breaking down the components of this average in our modified framework shows that enhancement is unlikely to be driving these cycles but is likely to be influencing the effects of other drivers.

2. Model 1: Two serotype SIR model with partial cross-enhancement

We now introduce our new framework for modelling cross-enhancement by modifying the conventional two-serotype SIR model with enhancement of transmission (Ferguson et al., 1999a; Adams and Boots, 2006). This model does not permit co-infection and so can be written as five intersecting compartments or, as here, eight disjoint compartments (Fig. 1a) corresponding to: susceptible to both serotypes (S_0), primary infected with serotype i (I_i), susceptible to secondary infection with serotype i (S_i), secondary infected with serotype i ($I_{j,i}$), immune to both serotypes (R). Natural mortality occurs at rate μ in all compartments. Individuals susceptible to both serotypes are born at rate μN to maintain a constant population size N. The vector population is not explicitly modelled. The immune cross-reaction acts on transmission. So susceptible individuals are infected with serotype i at rate $\lambda_i = \beta_0(I_i + \sigma I_{j,i})/N$ where β_0 is the transmission rate, $0 < \sigma < 1$ corresponds to cross-protection and $\sigma > 1$ corresponds to cross-enhancement. All infected individuals recover at rate γ. Those that recover from a primary infection become susceptible to secondary infection, those that recover from a secondary infection become immune to all further infections. No additional mortality is associated with any infection.

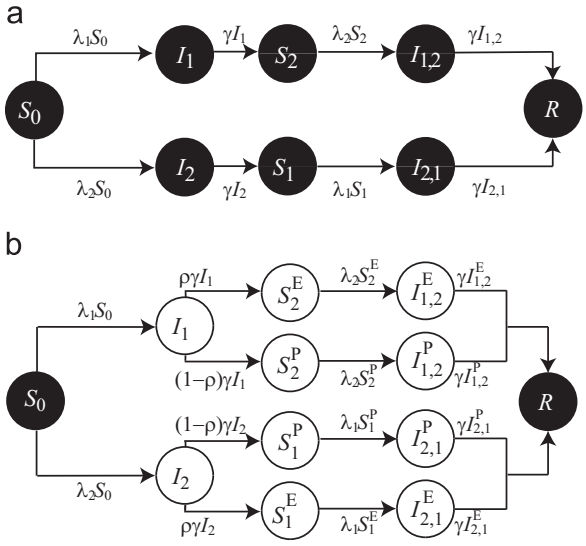

Fig. 1. Flow diagrams showing (a) the conventional structure for two serotype SIR models with cross-protection or cross-enhancement with intensity σ acting on transmission and (b) the modified structure incorporating partial cross-enhancement with prevalence ρ and intensity χ and partial cross-protection with prevalence $1-\rho$ and intensity η. For clarity demographic turnover has been omitted from both diagrams.

Our revised framework splits each of the secondary susceptible compartments S_i into two (Fig. 1b): those that are susceptible to secondary infection with immune cross-reaction enhancing transmission S_i^E and those that are susceptible to secondary infection with immune cross-reaction reducing transmission S_i^P. This split carries through to the secondary infected compartments $I_{j,i}^P$ and $I_{j,i}^E$. We define ρ to be the prevalence of enhancement. After a primary infection, a proportion ρ become susceptible to secondary infection with enhancement increasing their transmissibility when infected. A proportion $1-\rho$ become susceptible to secondary infection with partial protection reducing their transmissibility. Then individuals susceptible to primary or secondary infection with serotype i are infected at rate $\lambda_i=\beta_0(I_i+\eta I_{j,i}^P+\chi I_{j,i}^E)/N$ where $\chi>1$ is the intensity of enhancement and $0\le\eta\le 1$ is the degree of protection. This formulation means that, relative to the transmission rate β_0 of primary infections, the transmission rate of secondary infections is increased by a factor χ in enhanced individuals and decreased by a factor η in protected individuals. The system is therefore given by

$$\begin{aligned}
\dot{S}_0 &= \mu-(\lambda_1+\lambda_2+\mu)S_0,\\
\dot{I}_1 &= \lambda_1 S_0-(\gamma+\mu)I_1,\\
\dot{S}_2^E &= \rho\gamma I_1-(\lambda_2+\mu)S_2^E,\\
\dot{S}_2^P &= (1-\rho)\gamma I_1-(\lambda_2+\mu)S_2^P,\\
\dot{I}_{1,2}^E &= \lambda_2 S_2^E-(\gamma+\mu)I_{1,2}^E,\\
\dot{I}_{1,2}^P &= \lambda_2 S_2^P-(\gamma+\mu)I_{1,2}^P,\\
&\vdots\\
\dot{R} &= \gamma(I_{2,1}^E+I_{2,1}^P+I_{1,2}^E+I_{1,2}^P)-\mu R
\end{aligned}$$

with the omitted equations defined in the obvious way. Parameter definitions and values are given in Table 1.

The model splits the population into those prone/not prone to enhanced secondary infection at the point of recovery from primary infection. Alternatively, all individuals susceptible to secondary infection with a given serotype could be considered identical and the occurrence, or not, of enhancement determined when an individual succumbs to a secondary infection. It is thought that *FCγ* receptors are important for determining the occurrence of DHF. The *FCγRIIa* receptor has been associated with severe disease whereas the *RR* variant has been associated with subclinical infection (Garcíá et al., 2010; Loke et al., 2002). Polymorphisms at some HLA loci may also be important determinants of DHF susceptibility (Sierra et al., 2007; Mathew and Rothman, 2008). So we split the population at the point of recovery because it corresponds best to genetic predisposition to enhancement.

Table 1
Parameter definitions and values for models considered in this study. Where possible these have been taken from the corresponding conventional models (Ferguson et al., 1999a; Adams et al., 2006; Wearing and Rohani, 2006). All rates are per year.

Parameter	Definition	Model 1	Model 2	Model 3
N	Total population size	1	1	10^6
μ	Birth and death rate	0.02	0.017	0.02
γ	Recovery rate	99.98	52	60.8
ρ	Prevalence of enhancement	0–1	0–1	0–1
χ	Intensity of enhancement	1–∞	1–∞	1–∞
η	Degree of cross-protection	0–1	0–1	0–1
β_0	Baseline transmission rate	200	120	70
δ_1	Baseline transmission seasonality amplitude	–	0.1	–
Φ	Random variation in seasonality amplitude	–	1–1.25	–
σ_H	Host infection activation rate	–	–	73
δ_2	Temporary cross-protection loss rate	–	–	2–365
σ_V	Vector infection activation rate	–	–	36.5
a	Vector birth rate seasonality amplitude	–	–	0.05
μ_V	Vector death rate/baseline birth rate	–	–	26.1
k	Average number female vectors per host	–	–	2

In the conventional model framework, the intensity of enhancement σ is often taken as a bifurcation parameter. For σ less than 1, there is a stable endemic equilibrium solution. As σ increases above 1 a Hopf bifurcation soon occurs indicating a transition to oscillatory solutions. Initially these solutions are periodic but when σ is increased further, period doubling quickly leads to chaos (Ferguson et al., 1999a; Adams and Boots, 2006). The Hopf bifurcation divides the parameter space into regions in which the system exhibits non-oscillatory and oscillatory behaviours. The oscillatory behaviour has been associated with observed epidemiological patterns. So, for our modified model we are interested in using the equivalent Hopf bifurcation to identify regions of the parameter space defined by ρ (enhancement prevalence), χ (enhancement intensity) and η (degree of protection if not enhanced) in which the system is expected to oscillate. Recall that if $\rho=1$ everyone is prone to enhanced secondary infections, η is irrelevant and the system is equivalent to the conventional model with $\chi=\sigma$. If $\rho=0$ no-one is prone to enhanced secondary infection, χ is irrelevant and the system is equivalent to the conventional model with $\eta=\sigma$.

Fig. 2a shows, for different enhancement intensities χ, how the system behaviour changes as the enhancement prevalence ρ decreases from 1 to 0. If $\chi=2$ the endemic equilibrium is stable for $\rho=1$, and remains so as ρ decreases. If the enhancement intensity is higher, $\chi=3$ or $\chi=5$ the system exhibits chaotic oscillations for $\rho=1$. As ρ decreases, chaos is replaced with periodic oscillations and then the endemic solution becomes stable at a Hopf bifurcation. More intense enhancement results in chaotic oscillations persisting at lower enhancement prevalences. System behaviour depends on ρ and χ in a qualitatively similar way regardless of the degree of cross-protection in the population not prone to enhanced infection (Fig. 2a shows $\eta=1$, Figure S1 in the Supplementary Information shows $\eta=0.5$ and 0). Quantitatively, if cross-protection is weaker (higher η), for any given enhancement intensity χ, oscillations persist at lower enhancement prevalence ρ.

Fig. 2b shows the location of the Hopf bifurcation in the enhancement prevalence–intensity (ρ–χ) parameter space. The system is oscillatory to the left of the lines, non-oscillatory to the right. Note the log scale on the vertical axis. As enhancement prevalence (ρ) decreases the enhancement intensity required for the system to become oscillatory increases very rapidly. The boundary between the oscillatory and non-oscillatory regions is qualitatively similar regardless of the degree of cross-protection in the population not prone to enhancement. Quantitatively, if cross-protection is stronger (lower η), oscillations require higher enhancement prevalences (ρ) and/or intensities (χ). In all cases, if enhancement prevalence is less than 20%, the system is non-oscillatory unless the enhancement increases transmission by at least an order of magnitude.

Our modified framework only shows persistent oscillations if the proportion of the population that is prone to enhanced secondary infection is large or the transmission increase in those prone to enhanced infections is very high. It is, however, reasonable to ask if the conventional framework provides an acceptable approximation to our new framework if the 'average' cross-reaction in the population is the same in both models. To investigate this we define the expected cross-reaction $\overline{\chi}=\rho\chi+(1-\rho)\eta$. If η is fixed then χ can be determined as a function of ρ such that the expected cross-enhancement is the same for all enhancement prevalences (see Figure S2a in the Supplementary Information). The value of η was fixed at 11 values between 0 and 1. For each value of η, the location of the Hopf bifurcation in the enhancement prevalence–intensity (ρ–χ) parameter space was found, and the corresponding expected

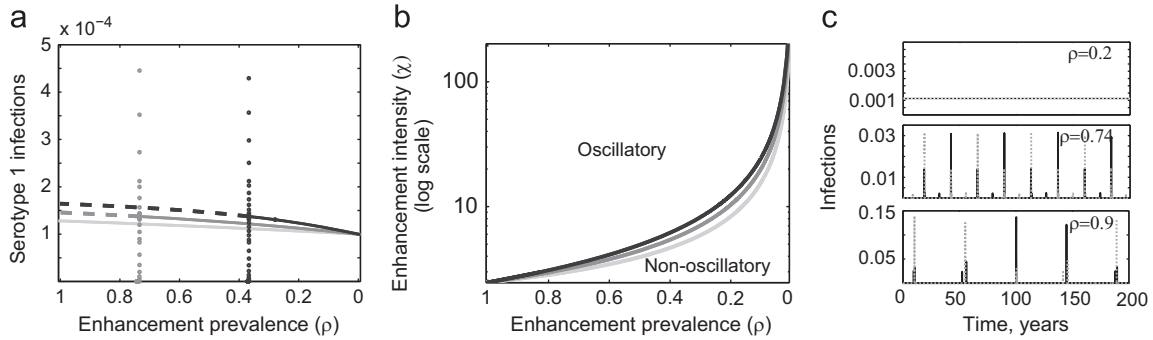

Fig. 2. Bifurcation diagrams for the two serotype SIR model with partial cross-enhancement acting on transmissibility. (a) Proportion of population infected with serotype 1 ($I_1+I_{2,1}^P+I_{2,1}^E$) depending on enhancement prevalence ρ. Solid lines correspond to stable equilibria, dashed lines to unstable equilibria and circles to stable periodic solutions. Where no stable solution is shown chaotic oscillations are expected. Shade corresponds to enhancement intensity. Black: $\chi=5$; dark grey: $\chi=3$; pale grey: $\chi=2$. The population not prone to enhancement does not gain any cross-protection ($\eta=1$), (b) location of the Hopf bifurcation dividing oscillatory and non-oscillatory asymptotic system behaviour in the ρ–χ (enhancement prevalence–intensity) parameter space. Shade corresponds to the degree of cross-protection in the population not prone to enhancement. Black: $\eta=0$; dark grey: $\eta=0.5$, pale grey: $\eta=1$. Note the vertical axis uses a log scale and (c) examples of typical behaviour for enhancement prevalence $\rho=0.2, 0.74, 0.9$ with $\chi=3, \eta=1$. (a) and (b) were computed using AUTO via Xppaut. Parameters were as in Table 1.

cross-enhancement calculated. In all cases the expected enhancement at the bifurcation point was, strikingly, identical.

3. Model 2: Two serotype SIR model with stochastic seasonality and partial cross-enhancement

Here we consider the implications of our new framework for cross-enhancement in the context of a seasonally forced model with stochastic variation in the forcing amplitude (Adams et al., 2006). The compartment system is similar to model 1, but enhancement and protection increase or decrease susceptibility rather than transmission, and co-infection is permitted. The co-infected state requires that the population is split into groups susceptible to enhanced and protected secondary infections at the primary infection stage (I_i), but otherwise the basic model structure is the same. The key parameters ρ, χ and η are defined as before. The main difference between model 2 and model 1 is the transmission rate. In model 2, the transmission rate varies seasonally $\beta(t)=\beta_0(1+\delta_1\Phi\ \sin(2\pi t))$, reflecting seasonal variation in vector density and competence, where the amplitude of this seasonal variation $\delta_1\Phi$ is subject to biannual random variation. Therefore the model equations are given by

$$
\begin{aligned}
\dot{S}_0 &= \mu-(\lambda_1+\lambda_2+\mu)S_0,\\
\dot{I}_1^E &= \rho\lambda_1 S_0-\chi\lambda_2 I_1^E-(\gamma+\mu)I_1^E,\\
\dot{I}_1^P &= (1-\rho)\lambda_1 S_0-\eta\lambda_2 I_1^P-(\gamma+\mu)I_1^P,\\
\dot{I} &= \chi(\lambda_1 I_2^E+\lambda_2 I_1^E)+\eta(\lambda_1 I_2^P+\lambda_2 I_1^P)-(2\gamma+\mu)I,\\
\dot{S}_2^E &= \gamma I_1^E-(\chi\lambda_2+\mu)S_2^E,\\
\dot{S}_2^P &= \gamma I_1^P-(\eta\lambda_2+\mu)S_2^P,\\
\dot{I}_{1,2} &= \chi\lambda_2 S_2^E+\eta\lambda_2 S_2^P+\gamma I-(\gamma+\mu)I_{1,2},\\
&\vdots\\
\dot{R} &= \gamma(I_{2,1}+I_{1,2})-\mu R
\end{aligned}
$$

with

$$\lambda_1=\frac{\beta(t)(I_1^E+I_1^P+I+I_{2,1})}{N}$$

and Φ re-assigned with a uniformly distributed random number between 1 and 1.25 whenever t is such that $\sin(2\pi t)=0$. The omitted equations are defined in the obvious way. Parameter definitions and values are given in Table 1.

Setting $\rho=0$ regains the conventional model with the parameter η determining the cross-reactive state of all secondary susceptible individuals. As usual, values $0\le\eta\le1$ correspond to cross-protection. Allowing $\eta>1$ would correspond to cross-enhancement. The stochastic variation in the seasonal forcing prevents the system from converging to a regular periodic solution in any region of parameter space. Instead the conventional system shows three generic behaviours, depending on the value of η. In addition to the seasonal oscillation directly associated with the forcing, serotype prevalence may show underlying oscillations with a multi-annual period and serotypes in phase, oscillations with a longer multi-annual period and serotypes out of phase, or chaotic oscillations characterised by very large, infrequent epidemics and no discernible phase structure (Adams et al., 2006), Fig. 3c. Empirical data have been associated with an out of phase serotype pattern. In the conventional model framework, out of phase patterns occur when η is in a narrow band around 0.4, representing a moderate degree of cross-protection. Other values of η give in phase patterns or, if η is allowed to be sufficiently greater than 1, chaos.

For our modified model we are interested in how enhancement prevalence ρ and intensity χ affect the occurrence of out of phase serotype patterns. When $\rho=0$ out of phase oscillations occur for η around 0.4 (Fig. 3a,b). Increasing ρ introduces enhancement with intensity χ and reduces the prevalence of cross-protection. Consequently the region of the η parameter space for which out of phase patterns occur shifts toward zero. As ρ increases further the out of phase patterns disappear altogether, and chaotic patterns begin to appear for η close to 1. For a modest enhancement intensity $\chi=2$ the out of phase patterns are no longer evident when $\rho=0.3$. These changes are accelerated by higher enhancement intensities χ (Supplementary Information Figure S3). As before, we can also consider models with the same expected cross-reaction but different enhancement prevalences. For this model, χ was fixed and η was determined as a function of ρ to obtain a constant expected cross-protection ($\overline{\eta}\le1$). For some values of ρ the required value of η was negative and so that expected cross-reaction was unattainable (see Figure S2b in the Supplementary Information). For both χ values tested ($\chi=2, \chi=5$), out of phase oscillations always occur when the expected cross-protection is around 0.4, regardless of the enhancement prevalence (see Supplementary Information Figure S2c).

4. Model 3: Two serotype SIR model with temporary cross-protection and partial cross-enhancement

Here we consider the implications of our new framework for cross-enhancement in the context of a deterministic seasonally

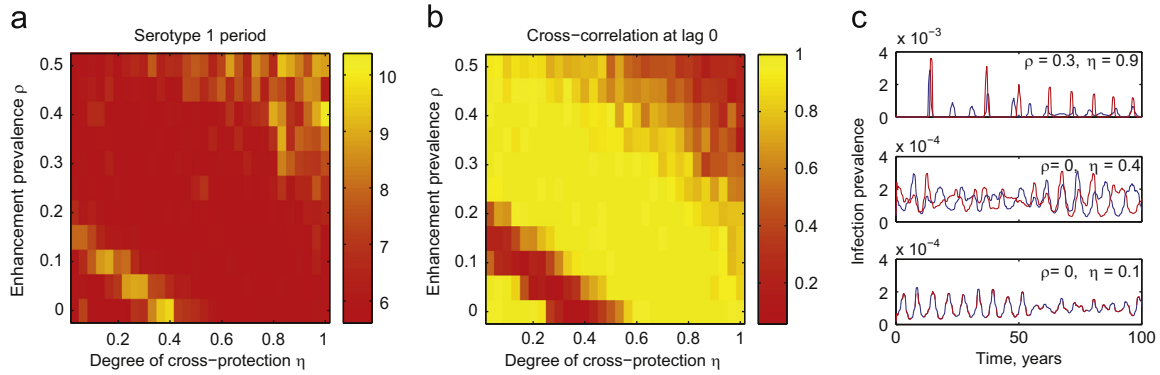

Fig. 3. Underlying epidemic period and cross-correlation of serotype prevalences depending on the prevalence of enhancement and degree of partial cross-protection in the model with stochastic seasonality. (a) Underlying epidemic period of serotype 1. The corresponding diagram for serotype 2 is very similar, (b) cross-correlation between prevalences of serotype 1 and serotype 2 at lag 0. Lower values indicate more out of phase patterns and (c) examples of the three types of behaviour typically displayed by the system: large, chaotic oscillations; out of phase oscillations with period around 10; in phase oscillations with period around 6. The initial condition was the serotype 1 only endemic equilibrium of the non-seasonal model. The system was solved with stochastic perturbation for a random time of between 0.5 and 1.5 years, then serotype 2 was introduced at very low prevalence and the system solved for 5000 years before output time series were generated. All figures are derived from 100 year time series of the total prevalence of each serotype ($I_i^E+I_i^P+I+I_{j,i}$), smoothed using a moving average method to remove seasonality. The dominant period was determined from the power spectrum. Each point in (a) and (b) is the average of 20 independent model realisations. Enhancement intensity $\chi=2$. Other parameters as in Table 1.

forced model with an explicit vector population and, in the host, a period of latency and a period of temporary complete cross-protection following a primary infection (Wearing and Rohani, 2006). The host part of the model can be formulated with compartments corresponding to the states susceptible to both serotypes (S_0), latent primary infection with serotype i (E_i), active primary infection with serotype i (I_i), temporary cross-protection against serotype i (C_i), susceptible to secondary infection with serotype i (S_i), latent secondary infection with serotype i ($E_{j,i}$), active secondary infection with serotype i ($I_{j,i}$) and immune to both serotypes (R). Our new framework for modelling enhancement splits the secondary susceptible compartment S_i into S_i^E and S_i^P. The key parameter is the duration of temporary complete cross-protection $1/\delta_2$. The model equations are therefore given by

$$\dot{S}_0 = N\mu-(\lambda_{V1}+\lambda_{V2}+\mu)\frac{S_0}{N},$$
$$\dot{E}_1 = \lambda_{V1}\frac{S_0}{N}-(\sigma+\mu)E_1,$$
$$\dot{I}_1 = \sigma E_1-(\gamma+\mu)I_1,$$
$$\dot{C}_1 = \gamma I_1-(\delta_2+\mu)C_1,$$
$$\dot{S}_2^E = \rho\delta_2 C_1-\chi\lambda_{V2}\frac{S_2^E}{N}-\mu S_2^E,$$
$$\dot{S}_2^P = (1-\rho)\delta_2 C_1-\eta\lambda_{V2}\frac{S_2^P}{N}-\mu S_2^P,$$
$$\vdots$$
$$\dot{R} = \gamma(I_{2,1}^P+I_{2,1}^E+I_{1,2}^P+I_{1,2}^E)-\mu R,$$
$$\dot{V}_{S1} = kNb(t)\mu_V-(\lambda_{H1}+\mu_V)V_{S1},$$
$$\dot{\epsilon}_{V1} = \lambda_{H1}V_{S1}-(\sigma_V+\mu_V)\epsilon_{V1},$$
$$\dot{\lambda}_{V1} = \beta_0\sigma_V\epsilon_{V1}-\mu_V\lambda_{V1},$$

with

$$\lambda_{H1} = \frac{\beta_0(I_1+I_{2,1}^E+I_{2,1}^P)}{N},$$
$$b(t) = 1-a\cos(2\pi t)$$

and the omitted equations defined in the obvious way. The state variables for the vector population overlap. V_{S1}, V_{S2} are the susceptible populations, ϵ_{V1}, ϵ_{V2} are the forces of latency, λ_{V1}, λ_{V2} are the forces of infection, and $b(t)$ is the seasonally varying birth rate. Parameter definitions and values are given in Table 1.

In the conventional model framework the duration of temporary cross-protection ($1/\delta_2$) and the intensity of enhancement (χ) determine the behaviour of the system. When cross-protection is brief ($1/\delta_2$ small) and enhancement intensity is low (χ small) the system exhibits annual oscillations (Fig. 4a). Increasing the enhancement intensity χ sufficiently leads to 'enhancement-induced' multi-annual oscillations. Alternatively, increasing the duration of cross-protection ($1/\delta_2$) sufficiently leads to 'immunity-induced' multi-annual oscillations. If the duration of cross-protection is such that immunity-induced oscillations occur, increasing the enhancement intensity decreases their period. Empirical data have been associated with oscillations of period around 3 in the aggregated time series for all serotypes. In the conventional model, aggregate oscillations with periods between 2 and 5 occur for a wide range of cross-immunity durations and enhancement intensities (Supplementary Information Figure S5a), although dynamics of each serotype may show oscillations with periods from 2 to 10 (Wearing and Rohani, 2006).

For our modified model we are interested in how enhancement prevalence (ρ) and enhancement intensity χ interact with the duration of temporary cross-protection to determine the period of oscillations. We first consider $\eta=1$, so individuals that are not prone to enhanced secondary infection do not have any protection against secondary infection either. Setting $\rho=1$ regains the original model. As enhancement prevalence ρ is reduced, the enhancement intensity required for enhancement induced multi-annual oscillations increases, beyond the range we considered (Fig. 4b). The duration of cross-protection required for immunity-induced oscillations increases slightly as enhancement prevalence decreases. This effect is more pronounced when enhancement intensity is higher. There is little change in the period of immunity-induced oscillations, when they occur, either for each serotype individually (Fig. 4c) or the aggregate of both serotypes (Supplementary Information Figure S5). We now consider $\eta=0$, so individuals that are not prone to enhanced secondary infection have complete protection against secondary infection. In this case, as enhancement prevalence ρ is reduced, the duration of cross-protection required for immunity-induced oscillations increases markedly (Fig. 4d–f). This effect is more pronounced when enhancement intensity is lower. The period of immunity-induced oscillations, when they occur, is generally higher and there is a sharper transition from period 1 oscillations to high period oscillations. This pattern is seen in the time series for the prevalence of each serotype individually, and when aggregated (Supplementary Information Figure S5). It is interesting that the onset of immunity-induced oscillations requires longer durations of temporary cross-protection at high enhancement intensities

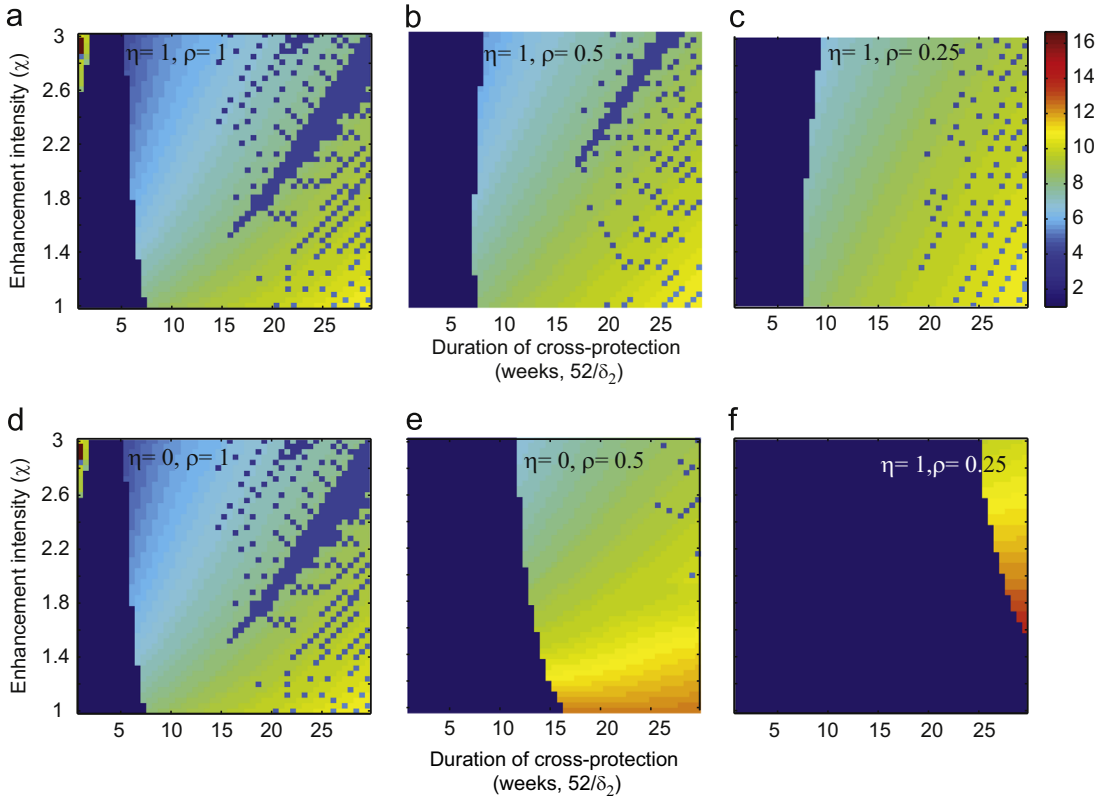

Fig. 4. Dominant period of oscillations in serotype 1 prevalence depending on duration of temporary cross-protection ($1/\delta_2$), enhancement intensity χ and enhancement prevalence ρ. (a–c) Individuals not prone to enhancement are not protected against secondary infection, $\eta = 1$. (d–f) Individuals not prone to enhancement are completely protected against secondary infection, $\eta = 0$. Note that when $\rho = 1$, the parameter η is redundant. In all cases the system was solved for 2500 years from an initial condition with 29% of the population fully susceptible and 71% fully recovered when infection is introduced. Then the dominant period was determined from the power spectrum of a 500 year time series of the total prevalence of serotype 1 ($I_1 + I^E_{2,1} + I^P_{2,1}$). Parameters as given in Table 1.

when permanent cross-protection (η) is weak, but at low enhancement intensities when permanent cross-protection is strong. The change occurs between η=0.2 and 0.1 (Supplementary Information Figure S4). Together, these results show that immunity-driven multi-annual oscillations are a complex product of the duration of temporary cross-protection, enhancement prevalence, enhancement intensity and the degree of permanent cross-protection. As with the previous models, the expected cross-enhancement can be held constant as ρ varies by fixing η and determining χ as a function of ρ. If the duration of temporary cross-protection is fixed at $1/\delta_2 = 15$ weeks, there is no permanent cross-protection ($\eta = 1$) and the expected cross-enhancement is close to 1, the system shows similar oscillations regardless of the prevalence of enhancement (See Supplementary Information Figure S2d). As the expected cross-enhancement increases away from 1, changing the enhancement prevalence leads to some small variation in the period of oscillations. This effect is more pronounced when the duration of temporary cross-protection is longer.

5. Discussion and conclusions

It is conventional to model immune cross-enhancement with a two serotype SIR model in which all individuals that recover from a primary infection become susceptible to enhanced secondary infection. In this study we noted data that suggest only a small proportion of primary infected individuals become susceptible to enhanced secondary infection, and modified three variants of the conventional model to reflect this observation. In the conventional enhancement framework, basic two serotype models (e.g. Ferguson et al., 1999a; Adams and Boots, 2006) require just a small enhancement of susceptibility or transmission to show persistent oscillatory dynamics. In our modified partial cross-enhancement framework, for all enhancement prevalences the basic two serotype model shows persistent oscillatory behaviour at the same threshold of the average cross-reaction in the whole population. However, decomposing the expected enhancement into weighted components of protection and enhancement shows that oscillations only occur if the proportion of the population that is prone to enhanced secondary infection is large or the transmission increase in those prone to enhanced infections is very high. These results weaken the hypothesis that ADE is driving the oscillatory dynamics of dengue. Alternative hypotheses include stochastic seasonality (Adams et al., 2006) and a period of temporary complete cross-immunity following a primary infection (Wearing and Rohani, 2006). We rendered the models used to support these hypotheses in our partial cross-enhancement framework and re-evaluated their behaviour.

In the conventional enhancement framework, a model in which stochastic seasonality drives multi-annual epidemic oscillations (Adams et al., 2006) predicts that two serotypes will have regular out of phase epidemic oscillations only when all secondary susceptible individuals have moderate partial protection against infection. Enhancement leads to highly irregular oscillations. In our modified partial cross-enhancement framework, for all enhancement prevalences, these out of phase oscillations occur over the same range of values for the average cross-protection in the population. Considering the components of the expected cross-protection shows that, as the prevalence of enhancement increases, out of phase oscillations require stronger partial protection against secondary infection in the population group not prone to enhancement. If there is a moderate to high prevalence of enhancement out of phase epidemic oscillations do not occur. So, our partial cross-enhancement framework neither supports nor refutes the hypothesis that stochastic seasonality is driving the oscillatory

dynamics of dengue. It does, however, indicate that partial cross-enhancement may be interacting with a seasonal driver to influence the period and phase structure of the epidemic oscillations.

In the conventional enhancement framework, a sufficiently long period of temporary but complete cross-protection between serotypes can drive multi-annual epidemic oscillations. The long-term immune interaction, whether partial cross-protection or cross-enhancement, influences the period of these oscillations (Wearing and Rohani, 2006; Aguiar et al., 2011). In our modified partial cross-enhancement framework, temporary complete cross-protection still drives multi-annual oscillations. The period of these oscillations only shows a mild response to the enhancement prevalence if the average cross-reaction in the population does not change. However, considering the components of the expected cross-reaction shows that the prevalence of enhancement in the secondary susceptible population and the degree of long-term partial cross-protection in the remainder of that population interact to have a strong impact on the duration of temporary cross-protection required for multi-annual oscillations. These factors also affect the period of such oscillations. So, our partial cross-enhancement framework neither supports nor refutes the hypothesis that temporary cross-protection is driving the oscillatory dynamics of dengue. It does, however, indicate that there is a complex interaction between this driver and the long-term immunological interactions which may be influencing the epidemic oscillations.

In this study we have argued that the conventional framework for modelling cross-enhancement between dengue serotypes should be modified to account for the observation that only a small proportion of the secondary susceptible population is actually prone to enhancement. We have shown that models modified in this way generally produce similar dynamical behaviour to conventional models if they are parameterised to have the same average cross-reaction over the whole population. However, breaking down the average cross-reaction into its constituent parts reveals that apparently reasonable values for the average cross-reaction may be underpinned by parameterisations that are difficult to justify. Most notably, when the enhancement prevalence is low, the individual enhancement intensity needs to be very high to achieve enhancement on average over the whole population. Consequently, insights from models with conventional enhancement frameworks should be re-evaluated. Future modelling studies that include dengue serotype cross-reaction, and particularly those involving estimation of immune cross-reaction parameters, should employ a partial cross-enhancement framework.

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Appendix A. Supplementary Information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jtbi.2014.02.016.

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